



Viewpoint

Hypertension Guidelines: Effect of Blood Pressure Targets

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ABSTRACT

There has been an abundance of hypertension guidelines over the years. Their purpose is to convey evidence-based findings from clinical trials to clinicians so that best medical choices can be made for the diagnosis and treatment of patients with hypertension. Over the past 3 years new hypertension guidelines have been published in the United States, Canada, Europe, and elsewhere with new or refined recommendations made regarding diagnosis, therapy, and intensity of treatment. Previous national guidelines were generally well aligned. However, there are major differences in the current North American and European recommendations in terms of the classification of hypertension and treatment goals, with the diagnosis of hypertension starting at 140/90 mm Hg for the European guidelines and 130/80 mm Hg for the American and Canadian guidelines. An important controversial aspect in the updated guidelines relates to a lowered threshold (130/80 mm Hg) at which hypertension is diagnosed and treated, because growing evidence indicates that individuals at low cardiovascular risk might be exposed to incremental harm because of overtreatment with antihypertensive drugs. However, these concerns need to be weighed against the robust evidence from the landmark Systolic Blood Pressure Intervention Trial (SPRINT) study and numerous meta-analyses, which clearly showed that intensive blood pressure-lowering aimed at a systolic blood pressure of 120–130 mm Hg causes a significant, > 25% reduction in cardiovascular morbidity

RÉSUMÉ

De nombreuses lignes directrices sur le traitement de l'hypertension ont été publiées au fil des ans. Leur objectif est notamment de faire part aux cliniciens des données probantes issues des essais cliniques afin qu'ils puissent prendre les meilleures décisions possible pour le diagnostic et le traitement des patients atteints d'hypertension. Au cours des trois dernières années, de nouvelles lignes directrices sur le traitement de l'hypertension ont été publiées aux États-Unis, au Canada, en Europe et ailleurs dans le monde, et présentent des recommandations nouvelles ou améliorées concernant le diagnostic, le traitement et l'intensité du traitement. Auparavant, les lignes directrices nationales étaient généralement bien harmonisées. Cependant, les recommandations actuellement en vigueur en Amérique du Nord et en Europe diffèrent considérablement sur le plan de la classification de l'hypertension et des objectifs de traitement; en effet, les lignes directrices européennes recommandent un diagnostic d'hypertension à partir de 140/90 mmHg et les lignes directrices américaines et canadiennes, à partir de 130/80 mmHg. L'un des aspects importants des nouvelles lignes directrices suscitant la controverse concerne l'abaissement à 130/80 mmHg du seuil auquel l'hypertension est diagnostiquée et traitée. Les données tendent en effet de plus en plus à démontrer que le surtraitement par des antihypertenseurs pourrait causer du tort aux personnes présentant un faible risque cardiovasculaire. De telles préoccupations doivent

Hypertension is the leading modifiable risk factor for disability and premature death from cardiovascular disease and accounts for approximately 10% of health care spending globally.^{1,2} Accordingly, blood pressure reduction should be a priority in every health care system. Considering the availability of a wide range of effective antihypertensive drugs that are well tolerated and generally affordable, it is surprising that in our modern society hypertension is so poorly controlled, with recent data indicating that in treated patients only approximately 30% achieve adequate blood pressure control.²⁻⁴ Chobanian, in his Shattuck lecture described this as the

“hypertension paradox” in which there is more uncontrolled disease despite improved therapy.⁵ Reasons for this are complex and multifactorial including poor adherence and compliance of drug treatment, therapeutic inertia, suboptimal therapy, and inadequate dosing.^{4,5} Further complicating these matters is the lack of clarity regarding optimal blood pressure targets, especially in hypertensive patients with comorbidities such as diabetes and kidney diseases, and in very elderly patients.^{2,6} The actual blood pressure thresholds at which treatment should be commenced and the target levels at which blood pressure should be maintained are a subject of intense discussion.⁷ To help address this, guidelines have been developed by experts to guide clinicians in the diagnosis and management of hypertension.

Most major hypertension guidelines are evidence-based, dictated by randomized controlled trial data and observational clinical studies.⁸ Recommendations are made to enable busy practitioners to follow best practice, establish best standards of care, and provide appropriate and balanced treatment to patients. Guidelines are usually written by

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See page 567 for disclosure information.

and mortality. This review highlights some of the important discrepancies between the major current guidelines, with a focus on definitions and treatment goals of hypertension. The effect of lower blood pressure targets and intensive antihypertensive treatment on cardiovascular benefit and risk is also discussed.

experts who scrutinize the relevant published clinical studies and trials to produce evidence-based recommendations. However, despite the apparent rigour, not all guidelines are the same and this is most evident in comparing the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines⁹ with the current European hypertension guidelines.¹⁰ Important differences relate especially to definition of hypertension and blood pressure treatment targets.

Until fairly recently, hypertension was generally diagnosed as a sustained office blood pressure > 140/90 mm Hg, with clinical guidelines suggesting commencement of pharmacologic treatment when blood pressure exceeds this level. However, in 2017 the ACC/AHA reclassified hypertension by lowering the threshold for treatment from 140/90 mm Hg to 130/80 mm Hg.⁹ Moreover, these guidelines recommended that pharmacologic treatment should be initiated in patients with a blood pressure > 130/80 mm Hg who are at high risk, defined as individuals with existing cardiovascular disease, a calculated 10-year cardiovascular risk of > 10%, or those who have other risk factors (eg, kidney disease or diabetes). In all patients with a blood pressure > 140/90 mm Hg independent of risk factors, ACC/AHA guidelines suggest that treatment should be initiated. Similar recommendations were soon adopted by many other major national guidelines including Hypertension Canada¹² and the International Society of Hypertension/American Society of Hypertension.¹² The evidence underpinning the lower blood pressure targets was driven in large part by the **Systolic Blood Pressure Intervention Trial (SPRINT)**, which showed that intensive treatment to lower blood pressure targets is cardiovascular-protective.¹³ Various meta-analyses also showed benefit of intensive blood pressure-lowering. In a meta-analysis of > 44,000 patients, intensive blood pressure-lowering below 140 mm Hg was associated with improved cardiovascular and renal outcomes.¹⁴ In another study of > 613,000 participants, lowering blood pressure to a systolic blood pressure of < 130 mm Hg was associated with significantly reduced cardiovascular events and mortality.¹⁵

SPRINT

The SPRINT study was a ground-breaking trial that investigated the effects of intensive blood pressure therapy on risk of cardiovascular disease and events in patients with hypertension.¹³ The primary outcome was a composite of

cependant être soupesées en regard des données solides issues de l'étude déterminante **SPRINT (Systolic Blood Pressure Intervention Trial)** et de nombreuses méta-analyses, qui indiquent clairement qu'une intervention intensive visant à faire diminuer la pression artérielle pour atteindre une pression systolique de 120-130 mmHg entraîne une réduction significative de plus de 25 % de la morbidité et de la mortalité d'origine cardiovasculaire. Dans cette revue, nous faisons ressortir certaines des plus importantes divergences entre les principales lignes directrices en vigueur, en insistant sur les définitions et les objectifs du traitement de l'hypertension. Nous présentons en outre les effets d'une diminution des valeurs cibles pour la pression artérielle et des traitements antihypertenseurs intensifs sur les bienfaits et les risques cardiovasculaires.

heart failure, acute coronary syndrome, myocardial infarction, and stroke. The trial enrolled 9361 patients. Patients at least 50 years of age with at least 1 cardiovascular risk factor were randomly assigned to intensive treatment with a systolic blood pressure goal of < 120 mm Hg or standard treatment with a systolic blood pressure goal of < 140 mm Hg. The 5-year trial was terminated prematurely after 3.26 years because the primary composite outcome showed a significant reduction in the intensive treatment group, with a 25% relative risk reduction vs standard therapy. These findings underscored the implementation of intensive treatment of blood pressure to lower targets in the ACC/AHA and Hypertension Canada guidelines. It has been estimated that implementing such approaches could prevent 107,500 premature deaths from cardiovascular death annually.¹⁶

Hypertension Guidelines in North America and Europe

After the 2017 ACC/AHA recommendations, the 2018 European Society of Cardiology and the European Society of Hypertension (ESC/ESH) guidelines on the diagnosis and management of hypertension were published.¹² Although both reports were developed using similar evidence-based clinical data, the recommendations differ with respect to 2 main points: (1) the classification of hypertension; and (2) treatment goals. The ACC/AHA guidelines in the United States⁹ and the Hypertension Canada guidelines in Canada¹¹ lowered the threshold for hypertension to 130/80 mm Hg, whereas guidelines in Europe, the United Kingdom, and other regions such as Australia¹⁶⁻¹⁸ have largely maintained traditional blood pressure categories, with grade 1 hypertension defined as an office blood pressure > 140/90 mm Hg. The ESC/ESH also introduced the concept of "safety boundaries," defined as treated systolic blood pressure not below 130 mm Hg in people older than 65 years and not below 120 mm Hg in people younger than 65 years. This cautious strategy is on the basis of concerns of potential adverse events associated with overtreatment with antihypertensive drugs and is supported by the findings of Bress et al.,¹⁹ who reported that over a 10-year period the number of cardiovascular events that would be prevented by intense blood pressure management would be similar to the number of serious adverse events. In response to these concerns, the American College of Physicians and the American Academy of Family Physicians (ACF/AAFP) developed their own guidelines for hypertension

management in the United States for adults older than 60 years, suggesting a blood pressure target of 150 mm Hg at which level treatment should be started.²⁰ Similar to the ESC/ESH guidelines and ACP/AAFP guidelines, the National Institute for Health and Clinical Excellence (NICE) guidelines also maintained a conservative approach.²¹ Current recommendations of NICE have not changed the definition of hypertension of 140/90 mm Hg from the previous iterations released in 2011 and updated in 2016 (<https://www.nice.org.uk/guidance/cg127>). The NICE guidelines of 2019 will be released in August 2019 (<https://www.nice.org.uk/guidance/indevelopment/gid-ng10054>) iteration.¹⁷

The Effect of Lower Diagnostic Thresholds on the Global Hypertension Burden

Redefining hypertension from 140/90 mm Hg to 130/80 mm Hg classifies previously “normotensive/prehypertensive” individuals as being “hypertensive,” who might require treatment. The effect of this on the hypertension burden nationally and globally is enormous, in terms of the prevalence of hypertension and the number of individuals requiring health care and antihypertensive therapy.²² By applying the new definitions, the prevalence of hypertension in adults younger than 45 years triples for men and doubles for women in the United States.²³ Numerous large studies further confirmed this in the general adult population. The **Reasons for Geographic and Racial Differences in Stroke (REGARDS)** study reported that adopting the 2107 ACC/AHA definitions would double the prevalence of hypertension worldwide.²⁴ Similar findings were shown in the **US National Health and Nutrition Examination Survey (NHANES)** and the **China Health and Retirement Longitudinal Study (CHARLS)**.²⁵ On the basis of diagnostic criteria of 140/90 mm Hg, the global prevalence of hypertension in adults is currently 30%-35%. However, applying the 2017 ACC/AHA or CHEP guidelines increases the global prevalence of hypertension in adults to > 60%. Associated with this, the number of patients requiring treatment would be doubled and those already receiving treatment would require intensification of pharmacotherapy. Hence, the potential effect of the hypertension burden on health care systems is significant.

Another important consideration with the lower threshold for diagnosing hypertension using the ACC/AHA or Hypertension Canada criteria, is at the individual patient level, in which people will be labelled as being hypertensive and unwell, although they might be at low risk of disease.^{26,27} This might adversely affect their sense of well-being and could have negative implications for personal health insurance and other concerns (eg, jobs) if they are considered to have a preexisting medical condition.²⁸

Effect of Guidelines on Benefits and Risks: Effects of Intensive Treatment

Collaborative meta-analysis of individual participant data from separate prospective studies clearly indicates that the relative risk of mortality due to cardiovascular disease in adults doubles with every 20 mm Hg increase in systolic blood pressure or 10 mm Hg increase in diastolic blood pressure.²⁹ This positive relationship holds true for systolic blood

pressures from as low as 115 mm Hg, below which there is little evidence. In 40- to 69-year-old adults, each difference of 20 mm Hg systolic blood pressure is associated with more than a twofold difference in the rate of death due to stroke, ischemic heart disease, and other vascular causes.²⁹ Hence, aggressive efforts at reducing blood pressure should be a priority to ensure good cardiovascular health and prevention of premature death due to cardiovascular disease. However, the level of blood pressure at which such treatment efforts should be initiated is currently a matter of deliberation.^{7,30}

It is predicted that implementing, achieving, and maintaining the ACC/AHA guideline goals could prevent 3 million cardiovascular disease events over 10 years compared with the number of events prevented using previous guidelines.¹⁹ However, these benefits might be associated with potential risks, especially related to serious adverse events of overtreatment with antihypertensive drugs. The forecast is that implementation of the 2017 ACC/AHA guidelines would not only prevent cardiovascular events but would also lead to approximately 3 million more treatment-related serious adverse events.¹⁹

Concerns have also been raised regarding the ACC/AHA recommendations in patients with mild hypertension and low cardiovascular risk and questions are being raised as to whether these individuals should be treated with antihypertensive drugs because there is a lack of supporting clinical evidence.^{31,32} This was recently addressed in a longitudinal cohort study using electronic health records from 38,286 low-risk patients with mild hypertension. Data were extracted from the Clinical Practice Research Datalink.³³ The study failed to show an association between exposure to antihypertensive treatment and mortality or cardiovascular disease. However, there was evidence that treatment might be associated with an increased risk of adverse events including hypotension, syncope, and acute kidney disease. Hence, antihypertensive treatment in low-risk patients with mild hypertension might have little benefit and might actually be associated with some harm.^{27,31}

Taken together these recent provocative studies emphasize the importance of weighing benefit vs risk and harm in treating patients aggressively to lower blood pressure targets, especially in those who have no or few risk factors. Guidelines simply provide recommendations; clinical judgement focusing on the need to individualize antihypertensive treatment, taking into account comorbidities and associated cardiovascular risk factors, should remain the basis of hypertension management.

Particular Controversies: Effect of Lower Blood Pressure Targets on Dementia and Chronic Kidney Disease

Dementia and cognitive impairment

A potential risk and clinical concern of overtreatment of hypertension is hypotension and cerebral hypoperfusion with consequent negative effects on the brain and cognition. The recent **Systolic Blood Pressure Intervention Trial (SPRINT) Memory and Cognition in Decreased Hypertension (MIND)** [SPRINT MIND] study, a substudy of SPRINT, specifically questioned whether intensive blood pressure control reduces

the occurrence of dementia.³⁴ Results showed that unlike beneficial effects on cardiovascular events, intensive blood pressure aimed at < 120 mm Hg compared with < 140 mm Hg did not significantly decrease the incidence of probable dementia. However, intensive blood pressure control was associated with a significant reduction in mild cognitive impairment, a risk factor for dementia. It should be highlighted that although dementia rates were not altered in SPRINT MIND, there was no evidence of cerebral hypoperfusion and no harm to cognition in patients treated to lower blood pressure levels. SPRINT was terminated early because of significant cardiovascular benefit, and accordingly the trial might have been underpowered to evaluate the primary adjudicated cognitive outcome of probable dementia. Perhaps had the trial extended beyond the 3.26 years, significant effects on probable dementia rates might have been evident. Whether the outcomes would be beneficial or harmful is unknown, but hopefully SPRINT patients will be followed long-term to gain better insights into dementia outcomes over time in this patient cohort. To support this the Alzheimers Association has awarded new funding. The trial is called SPRINT MIND 2.0. Although lower blood pressure was not associated with cognitive harm in SPRINT MIND, it should be emphasized that the trial did not focus on mean arterial pressure and pulse pressure, which are primary drivers of cerebral blood flow.³⁵

New 2-year funding from the Alzheimers Society will extend the SPRINT MIND trial to help clarify the impact of aggressive blood pressure treatment on the risk for dementia. The new trial is called SPRINT MIND 2.0.

Chronic kidney disease

Hypertension and chronic kidney disease are common comorbidities, with high mortality risk. Blood pressure-lowering is associated with reduced cardiovascular events in these patients.³⁶ However there is still deliberation about the optimal blood pressure and therapeutic goal. Guidelines differ on blood pressure targets with the 2017 ACC/AHA recommending a goal of < 130/80 mm Hg in patients with chronic kidney disease whereas the European guidelines favour a higher systolic blood pressure goal of 130-140 mm Hg. Numerous trials have examined effects of intensive blood pressure control on cardiovascular events and all-cause mortality in patients with hypertension and chronic kidney disease. Data from large meta-analyses have not been consistent, with some studies showing benefit only in patients with proteinuria³⁶ and others reporting clear benefit of more intensive blood pressure control in patients with stage 3-5 chronic kidney disease.³⁷ Some studies have reported worsening of renal disease with tighter blood pressure control, especially in patients with diabetes.³⁸⁻⁴⁰ In a case control study, incident chronic kidney disease in the setting of intensive systolic blood pressure-lowering was accompanied by decreases, rather than elevations, in levels of kidney damage biomarkers.⁴¹ A recent meta-analysis comprising 4 major trials (Modification of Diet in Renal Disease [MDRD]; African American Study of Kidney Disease and Hypertension [AASK]; Action to Control Cardiovascular Risk in Diabetes [ACCORD], and SPRINT) compared intensive vs standard blood pressure approaches. Results clearly showed that

intensive blood pressure management improves survival of patients with hypertension and chronic kidney disease, supporting the lower targets suggested by some current guidelines.⁴⁰ Nevertheless, within the context of high-risk patients with chronic kidney disease, treatment of hypertension should be adapted to each patient, taking associated risk factors into consideration.

Conclusions

Hypertension guidelines all have the same overall objective of communicating evidence-based data from clinical trials to practitioners, and providing recommendations for best clinical practice and best care for patients with hypertension. Despite the plethora of international, national, and regional guidelines, the prevalence of hypertension is high and control rates remain disappointingly low worldwide, because of many complex factors. The insufficiency of control is likely to worsen with changing definitions of hypertension and lower blood pressure treatment targets. The updated recommendations in Europe and the United Kingdom, together with the guidelines of the ACP/AAFP, are in general alignment that treatment of patients should aim at lowering blood pressure to 140/90 mm Hg.⁴² However, these guidelines are at odds with the current ACC/AHA and Hypertension Canada guidelines, which have lowered the threshold to 130/80 mm Hg. These disparities likely reflect a lack of consistent evidence from clinical trials and studies. The more conservative approach of the European and NICE guidelines are in large part on the basis of the potential risks and harm associated with intensive antihypertensive treatment to lower blood pressure targets whereas the ACC/AHA guidelines are driven by the proven benefit of intensive treatment shown by SPRINT, which unambiguously showed a 25% reduction of morbidity and death associated with cardiovascular disease, despite some risk of adverse events. Such discrepancies add confusion and challenges to diagnostic and treatment choices for the busy clinician managing patients with hypertension. From a pragmatic viewpoint, it should be underscored that guidelines are merely recommendations on the basis of the best available evidence whereas the central element in decision-making remains sound clinical judgement. Moreover, clinicians should strongly advocate and actively prescribe healthy lifestyle choices for all hypertensive patients independently of the systolic blood pressure and of whether or not they are receiving antihypertensive medication.

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